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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.	
08/319,411	10/06/1994	PETER NIELSEN	ISIS1158	8648	
32650 7	590 01/22/2004		EXAMINER		
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR			MARSCHEL, ARDIN H		
PHILADELPHIA, PA 19103			ART UNIT	PAPER NUMBER	
	·		1631		
			DATE MAILED: 01/22/2004	4	

Please find below and/or attached an Office communication concerning this application or proceeding.

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		Application No.	Applicant(s)			
· · · · · · · · · · · · · · · · · · ·		08/319,411	NIELSEN ET AL.			
Office Actio	n Summary	Examiner	Art Unit			
		Ardin Marschel	1631			
The MAILING DA Period for Reply	TE of this communication app	pears on the cover sheet wi	th the correspondence address			
THE MAILING DATE OF  Extensions of time may be available after SIX (6) MONTHS from the  If the period for reply specified a  If NO period for reply is specified.	extended period for reply will, by statute later than three months after the mailing	36(a). In no event, however, may a re y within the statutory minimum of thirt will apply and will expire SIX (6) MON c. cause the application to become AB	eply be timely filed  y (30) days will be considered timely.  THS from the mailing date of this communication  ANDONED (35 U.S.C. § 133).	ion.		
1) Responsive to cor	nmunication(s) filed on 2/20	/03, 7/15/03, <b>&amp;</b> 10/30/03.				
2a) This action is FINA		action is non-final.				
3) Since this applica						
Disposition of Claims						
4)⊠ Claim(s) <u>1,5,8-10,</u>	12,13,15,20,23,24,30-32,47	-49 and 51-62 is/are pendi	ng in the application.			
The state of the s	laim(s) <u>See Continuation Sh</u>					
5) Claim(s) is.	are allowed.					
6)⊠ Claim(s) <u>1,5,8-10,</u>	12,13,15,20,23,24,30-32,47	-49, & 51-62 is/are rejected	i.			
7) Claim(s) is.						
8) Claim(s) ar	e subject to restriction and/o	r election requirement.				
Application Papers						
, — ·	s objected to by the Examine					
			objected to by the Examiner.			
* *	equest that any objection to the					
			(s) is objected to. See 37 CFR 1.121			
•		kaminer. Note the attached	Office Action or form PTO-152.			
Priority under 35 U.S.C. §§						
a) ☐ All b) ☐ Some 1. ☐ Certified co	is made of a claim for foreign  * c) None of:  pies of the priority document  pies of the priority document	ts have been received.				
3. Copies of the application	ne certified copies of the prio from the International Burea etailed Office action for a list	rity documents have been u (PCT Rule 17.2(a)).	received in this National Stage			
13) Acknowledgment is since a specific refe 37 CFR 1.78.	made of a claim for domest rence was included in the fir	ic priority under 35 U.S.C. st sentence of the specific	§ 119(e) (to a provisional applica ation or in an Application Data St	ation) heet.		
	n of the foreign language pro			fic		
reference was inclu-	made of a claim for domest ded in the first sentence of the	ne specification or in an Ap	§§ 120 and/or 121 since a specification Data Sheet. 37 CFR 1.7	78.		
Attachment(s)						
1) Notice of References Cited		• ===	dummary (PTO-413) Paper No(s)	. •		
· <u></u>	tent Drawing Review (PTO-948) ement(s) (PTO-1449) Paper No(s) _	5) Notice of Ir	nformal Patent Application (PTO-152) .			

Continuation of Disposition of Claims: Claims (Claims: Claims Claims: Claims:

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# **DETAILED ACTION**

Applicants' arguments, filed 2/20/03, 7/15/03, and 10/30/03, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Upon reconsideration, unfortunately the following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

## SUBSTITUTE SPECIFICATION

The substitute specification, filed 7/15/03, has been approved for entry and has been entered.

## SCOPE OF ENABLEMENT

Claims 23, 24, 30-32, 47-49, and 57-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptide nucleic acid conjugates wherein the monomers are linked via amide or peptide bonds between the amino and carboxyl termini of each monomer therein, does not reasonably provide enablement for any covalent linkage practice between monomeric units. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in <u>Ex parte Forman</u>, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at

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1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

It is noted that instant claims 1 and 5 include the limitation that the backbone of the claimed PNA conjugate is formed via amide bonds which are reasonably interpreted as bonds made from covalent linkage between an amino and carboxyl terminus of each linked monomeric unit. Such peptide or amide bond type of linkages to form various PNA conjugate polymers are amply described regarding synthetic guidance in the specification via numerous examples of such chemical steps as needed. No other intermonomer linkage guidance is instantly set forth for making PNA oligomers from the cited monomers. Consideration of the instant independent claims 30, 47-49, and 57-62 reveals that monomeric units are set forth but without any limitation therein as to what linkage is practiced for the formation of the claimed PNA conjugate oligomers therein. The monomers as cited in the claims contain a number of well known active sites such as amino moieties, hydroxyls, carboxyls, and thiols. In order to control and direct oligomer synthesis to make a desired PNA oligomer, these groups must be considered

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and generally protected to prevent undesired covalent structures from forming. Such protecting groups must also be removed at the end of synthesis without breaking desired covalent structures of the PNA conjugates to obtain the desired results. These complex oligomer synthetic issues support unpredictability and a lack of enablement other than the amide or peptide linkage methodology with protection/deprotection steps as instantly claimed. Claims which are directly or indirectly dependent from the above listed independent claims also are included in this rejection due to their dependency.

#### **PRIOR ART**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 8-10, 15, 20, 23, 24, 30-32, 47-49, and 51-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah et al. (P/N 5,705,333); taken in view of each of the following references separately: Pasternak (P/N 5,234,579); Mrsny et al. (P/N 4,879,220); Fujii et al. [FEBS Lett. 97(1): 193(1979)]; Mechanic et al. [BBA 393:419(1975)]; and Lonsdate et al. (P/N 4,917,800).

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Shah et al. has been documented in previous office actions as setting forth the basic PNA structure as instantly claimed, as well as amended in the most recently submitted amendment to the instant claims directed to peptide linked amino acid type monomers, and that Shah et al. generically describes crosslinking agent containing PNA conjugates which is not predated by parental priority documents of the instant application. This generic crosslinking agent description is deemed to reasonably motivate and suggest the inclusion of crosslinking agents as described in the prior art. It is noted that the specific limitation of "crosslinking agent" has been removed from the instant claims via amendment. It, however, has been found that that the remaining conjugate moieties as listed in instant claim 1, last 2 lines, are crosslinking agents as evidenced by the above listed additional references which are summarized more in detail as follows.

Pasternak (P/N 5,234,579) in column 2, line 66, through column 3, line 7, describes a terpene which is a thermal crosslinker. This is also described in column 4, lines 6-35, wherein a terpene polymer is thermally cross-linked. It is noted that the instant claims do not described, nor the instant specification, as filed, any limiting definition of what is meant as a "crosslinking agent" which distinguishes over the the crosslinking practice as described in this reference which includes terpene in a crosslinking reaction.

Mrsny et al. (P/N 4,879,220) in column 3, lines 11-17, describes the practice of a probe which attaches to a cell receptor. In column 4, lines 20-61, the cell receptor probe is utilized in a crosslinking reaction indirectly with a specific crosslinking agent

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which thus describes a conjugated crosslinking agent which is a binding ligand for a cell receptor as cited also in instant claim 1. It is noted that the instant claims do not described, nor the instant specification, as filed, any limiting definition of what is meant as a "crosslinking agent" which distinguishes over the the crosslinking practice as described in this reference which includes a conjugated cell receptor binding ligand as in the reference in a crosslinking reaction.

Fujii et al. [FEBS Lett. 97(1): 193(1979)] on page 193, first column, lines 23-26, describes a water soluble vitamin, vitamin B6, as being an agent which controls or affects crosslink formation thus generically qualifying it as a crosslinking agent. It is noted that the instant claims do not described, nor the instant specification, as filed, any limiting definition of what is meant as a "crosslinking agent" which distinguishes over the the crosslinking practice as described in this reference which thus includes the water soluble vitamin, B6, as a crosslinking agent. It is also noted that the biochemical textbook, Lehninger, is cited herein only to support the concept that Vitamin B6 is a water soluble vitamin (See Table 13-3 in Lehninger at page 272.) as also required in instant claim 1, last two lines.

Similar to the above reference citation, Mechanic et al. [BBA 393:419(1975)] in the title describes Vitamin D as an effector of crosslinking. This is also described as the central conclusion in the DISCUSSION section on pages 423-424 of the reference. It is noted that the instant claims do not described, nor the instant specification, as filed, any limiting definition of what is meant as a "crosslinking agent" which distinguishes over the the crosslinking practice as described in this reference which includes the lipid soluble

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vitamin, vitamin D, in a crosslinking control reaction function. It is also noted that the biochemical textbook, Lehninger, is cited herein only to support the concept that Vitamin D is a lipid soluble vitamin (See the last full paragraph on page 204 in Lehninger.) as also required in instant claim 1, last two lines.

Lonsdate et al. (P/N 4,917,800) in claim 15 (in columns 13-14) therein describes a porphyrin which contains crosslinking groups and thus is a crosslinking agent. This is also described in column 9, lines 48-50, wherein a porphyrin monomers are cited as having functional groups which cause a film to be highly crosslinked. It is noted that the instant claims do not described, nor the instant specification, as filed, any limiting definition of what is meant as a "crosslinking agent" which distinguishes over the the crosslinking practice as described in this reference which thus includes porphyrin as a crosslinking agent.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the various crosslinking agents as cited above in the references directed to such agents as motivated and suggested generically to include such crosslinking agents in the PNA conjugates of Shah et al. to result in the practice of the above listed instant claims. Instant claim 5 also cites the above specifically described crosslinking agents in PNA conjugate embodiments. Applicants are also reminded that Shah et al. discloses other conjugates in a PNA structure which include nucleic acid cleavage groups of complexes in column 19, line 58, through column 20, line 13, as still claimed as RNA/DNA cleaving complex as in instant claim 5. Shah et al. in column 20, lines 6-14, cite a protein conjugate such as various nucleases

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as in instant claim 5. Also, a reporter molecule is reasonably described in Shah et al. as a label in column 19, line 24 and 46-50, as in instant claim 5. Also, PNA conjugate practice including polylysine conjugates are cited in Shah et al. in column 22, lines 47-51, as also required in instant claims 51 and 52. Instant claims 47, 49, 54, 56, and 59 are newly included in this rejection based on Shah et al. etc. because consideration of said claims 47, 49, 54, 56, and 59 reveals that they include the basic Shah et al. PNA-conjugate structure where the last line of claims 47, 49, 54, 56, or 59 regarding R group limitations is not required for all embodiments of either of claims 47, 49, 54, 56, or 59 as they are presently worded.

Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobberding et al. (P/N 5,623,049).

This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, because the reference cites cell recognition unit(s) in conjugate practice therein which is reasonably a cell receptor binding molecule as required in instant claims 1 and 5. In the reference in column 5, line 38, through column 6, line 4, other conjugates are listed such as carbohydrate, protein, or polypeptide (a peptide made up of many peptide units) as also are conjugate limitations in instant claim 5.

## **OBVIOUSNESS-TYPE DOUBLE PATENTING**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5, 8-10, 12, 13, 15, 20, 23, 24, 30-32, 47-49, 53-58, and 60-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,539,082. Although the conflicting claims are not identical, they are not patently distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, and additionally applied to appropriate newly submitted instant claims. Applicants argue that cross-linking agent has been removed from the claims thus making the rejection based on such practice as moot. In response, this removal of the crosslinking character of a Lysine moiety as a limitation of the instant claims has overcome this basis for this rejection. Applicants then argue that nucleobases cannot be interpreted as reporter molecules because they participate in Watson-Crick or Hoogstein type binding. In response none of the instant claims require any such participation or not. Further in response, whether participating or not in such a binding reaction, it is well known that nucleobases are detectable as labels in polymers which

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contain them thus still being deemed to be inclusive of common reporter molecule containing embodiments of both sets of claims as set forth above.

Claims 5, 8-10, 12, 13, 15, 20, 23, 24, 30-32, 47-49, 53-58, and 60-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,773,571. Although the conflicting claims are not identical, they are not patently distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, and additionally applied to appropriate newly submitted instant claims. Applicants argue that cross-linking agent has been removed from the claims thus making the rejection based on such practice as moot. In response, this removal of the crosslinking character of a Lysine moiety as a limitation of the instant claims has overcome this basis for this rejection. Applicants then argue, analogously to the above rejection, that nucleobases cannot be interpreted as reporter molecules because they participate in Watson-Crick or Hoogstein type binding. In response none of the instant claims require any such participation or not. Further in response, whether participating or not in such a binding reaction, it is well known that nucleobases are detectable as labels in polymers which contain them thus still being deemed to be inclusive of common reporter molecule containing embodiments of both sets of claims as set forth above.

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Claims 5, 8-10, 12, 13, 15, 20, 23, 24, 30-32, 47-49, 53-58, and 60-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, and 8 of U.S. Patent No. 5,786,461. Although the conflicting claims are not identical, they are not patently distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, and additionally applied to appropriate newly submitted instant claims. Applicants argue that cross-linking agent has been removed from the claims thus making the rejection based on such practice as moot. In response, this removal of the crosslinking character of a Lysine moiety as a limitation of the instant claims has overcome this basis for this rejection. Applicants then argue, analogously to the above rejection, that nucleobases cannot be interpreted as reporter molecules because they participate in Watson-Crick or Hoogstein type binding. In response none of the instant claims require any such participation or not. Further in response, whether participating or not in such a binding reaction, it is well known that nucleobases are detectable as labels in polymers which contain them thus still being deemed to be inclusive of common reporter molecule containing embodiments of both sets of claims as set forth above.

Claims 5, 8-10, 12, 13, 15, 20, 23, 24, 30-32, 47-49, 53-58, and 60-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 5,719,262. Although the

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conflicting claims are not identical, they are not patently distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, and additionally applied to appropriate newly submitted instant claims. Applicants argue that cross-linking agent has been removed from the claims thus making the rejection based on such practice as moot. In response, this removal of the crosslinking character of a Lysine moiety as a limitation of the instant claims has overcome this basis for this rejection. Applicants then argue, analogously to the above rejection, that nucleobases cannot be interpreted as reporter molecules because they participate in Watson-Crick or Hoogstein type binding. In response none of the instant claims require any such participation or not. Further in response, whether participating or not in such a binding reaction, it is well known that nucleobases are detectable as labels in polymers which contain them thus still being deemed to be inclusive of common reporter molecule containing embodiments of both sets of claims as set forth above.

Claims 5, 8-10, 12, 13, 15, 20, 23, 24, 30-32, 47-49, 53-58, and 60-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 5, and 7 of U.S. Patent No. 6,395,474. Although the conflicting claims are not identical, they are not patently distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

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This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, and additionally applied to appropriate newly submitted instant claims. Applicants argue that cross-linking agent has been removed from the claims thus making the rejection based on such practice as moot. In response, this removal of the crosslinking character of a Lysine moiety as a limitation of the instant claims has overcome this basis for this rejection. Applicants then argue, analogously to the above rejection, that nucleobases cannot be interpreted as reporter molecules because they participate in Watson-Crick or Hoogstein type binding. In response none of the instant claims require any such participation or not. Further in response, whether participating or not in such a binding reaction, it is well known that nucleobases are detectable as labels in polymers which contain them thus still being deemed to be inclusive of common reporter molecule containing embodiments of both sets of claims as set forth above.

Claims 5, 8-10, 12, 13, 15, 20, 23, 24, 30-32, 47-49, 53-58, and 60-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,414,112; taken in view of Summerton et al. (WO 86/05518). Although the conflicting claims are not identical, they are not patently distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, and additionally applied to appropriate newly submitted instant claims.

Applicants argue that cross-linking agent has been removed from the claims thus

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making the rejection based on such practice as moot. In response, this removal of the crosslinking character of a Lysine moiety as a limitation of the instant claims has overcome this basis for this rejection. Applicants then argue, analogously to the above rejection, that nucleobases cannot be interpreted as reporter molecules because they participate in Watson-Crick or Hoogstein type binding. In response none of the instant claims require any such participation or not. Further in response, whether participating or not in such a binding reaction, it is well known that nucleobases are detectable as labels in polymers which contain them thus still being deemed to be inclusive of common reporter molecule containing embodiments of both sets of claims as set forth above.

Claims 5, 8-10, 12, 13, 15, 20, 23, 24, 30-32, 47-49, 53-58, and 60-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,613,873. Although the conflicting claims are not identical, they are not patently distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

This rejection is reiterated and maintained from the previous office action, mailed 11/20/02, and additionally applied to appropriate newly submitted instant claims.

Applicants argue that cross-linking agent has been removed from the claims thus making the rejection based on such practice as moot. In response, this removal of the crosslinking character of a Lysine moiety as a limitation of the instant claims has overcome this basis for this rejection. Applicants then argue, analogously to the above

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rejection, that nucleobases cannot be interpreted as reporter molecules because they participate in Watson-Crick or Hoogstein type binding. In response none of the instant claims require any such participation or not. Further in response, whether participating or not in such a binding reaction, it is well known that nucleobases are detectable as labels in polymers which contain them thus still being deemed to be inclusive of common reporter molecule containing embodiments of both sets of claims as set forth above.

#### **INFORMALITIES**

The disclosure is objected to because of the following informalities:

In the substitute specification on page 13, line 30, the word "deravative" appears to be misspelled.

Appropriate correction is required.

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (571)272-0718. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571)272-0722.

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Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571)272-0549 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

January 20, 2004

ARDIN H. MARSCHEL PRIMARY EXAMINER

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